REMARKS

Amendments to the Specification

The specification has been amended to correct a clerical error in various formulas. Specifically, the α-ketoamide moiety **-CONH-** was inadvertently omitted from each formula listed at page 14, line 27, to page 17, line 11.

This amendment does not introduce new matter since the corrected formulas are readily apparent from the original specification. In particular, support for this amendment can be found in the main formula itself, Formula I (*see e.g.*, p. 9, l. 13). There it shows α-ketoamides represented by the formula M^1-AA^2-AA^1-CO-NR_3R_4. Similarly, at page 28, lines 3-4, a genus of α-ketoamides is represented by the formula M^1-Leu-AA-CONH-R^2. Hence both general formulas used in the application show the α–ketoamide moiety. Furthermore, the particulars of this convention, which is used throughout the specification and claims, are discussed at page 5, line 28, to page 6, line 2. In this section, Applicants use AK295 as an example and explain that AK295 is represented as Z-Leu-Abu-CONH-$(CH_2)_3$-4-morpholinyl. However, in the list of compounds at page 14, line 27, to page 17, line 11, AK295 is incorrectly shown as Z-Leu-Abu-$(CH_2)_3$-4-morpholinyl (*see* p. 15, l. 10). The omission of the α-ketoamide moiety –CONH– after the second amino acid residue is readily apparent and was inadvertently propagated throughout the list of compounds in this section of the specification. As such, Applicants have amended the specification to correct this error.

Amendments to the Claims

Claims 1-4 and 23-32 have been canceled and new Claims 33-39 have been added herein. Claims 33-39 are now pending.

Support for new Claim 33 can be found in original Claims 1 and 3, which have been canceled herewith, and in the specification at Table 4, at page 28, lines 3-4, and more generally at page 9, line 9, to page 11, line 2.

Support for new Claim 34 can be found in original Claim 4, which has also been canceled herewith, and in the specification at page 14, line 27, to page 17, line 11. The formulas recited in this new claim are the corrected formulas that show the α-ketoamide moiety –CONH–. Support for these corrected formulas is mentioned above where the amendments to the specification are discussed.

Support for new Claim 35 can also be found in original Claim 4 and in the specification at page 15, line 10.

Claim 32, which has been canceled herein, has been simply rewritten as new Claim 36.

Support for new Claims 37 and 38 can be found in the specification at, *inter alia*, page 14, lines 14-16 and 24-25.

Support for new Claim 39 can be found throughout the specification at page 18, lines 27-28, and page 18, line 33, to page 19, line 6.

No new matter has been added by these amendments; therefore, Applicants respectfully request that Examination continue on the claims as amended herewith.

Claims Rejections Under 35 U.S.C. § 103

The Examiner maintained the rejection of Claims 1-4 and 23-32 under 35 U.S.C. § 103(a), alleging that these claims are obvious over Saatman *et al.* (*Proc. Natl. Acad. Sci. USA* 93:3428, 1996) (hereinafter "Saatman") in view of Wang *et al.* (*J. Neuropathol. Exp. Neurol.* 59:599, 2000) (hereinafter "Wang") and Schaecher *et al.* (*Naurochem. Res.* 26:731, 2001) (hereinafter "Schaecher"). Since Claims 1-4 and 23-32 have been canceled herein, Applicants respectfully traverse this rejection to the extent that it may apply to new Claims 33-39.

Examiner's Comments Regarding Applicants' Prior Response

In maintaining the rejection, the Examiner first asserted that Applicants' prior arguments were not persuasive because the rejection was based on a combination of the cited references whereas Applicants allegedly attacked the cited references individually (Final Office Action, p. 2, ¶ 2). This was not the case. At the very outset of discussing the rejection under § 103, Applicants stated that "neither Saatman nor Wang, taken alone **or in combination**, teach the highlighted portion of claim 1 above" (Previous Response, p. 19, ll. 1-2; emphasis added). Similarly, Applicants later showed that "Wang, alone **or in combination** with Saatman, does not teach or suggest the claim method" (Previous Response, p. 19, ll. 19-20; emphasis added). To be precise, Applicants' arguments followed the outline set forth in *Graham v. John Deere Co.*, 383 U.S. 1 (1966), which requires, *inter alia*, an inquiry into the scope and content of the prior art and the differences between the prior art and the claimed subject matter. It is inaccurate to characterize Applicants' prior arguments as merely an attack of each reference individually and, thus, improper to dismiss their arguments on this basis. Applicants respectfully request that the prior arguments be reconsidered.

Secondly, the Examiner alleged that the prior arguments were not persuasive because Applicants contended that Saatman and Wang were non-analogous art (Final Office Action, p. 2, ¶ 2). Non-analogous art, which cannot be used to establish obviousness, is art that is not "within the field of the inventor's endeavor" or "reasonably pertinent to the particular problem with which the inventor was involved." *In re Wood*, 599 F.2d 1032, 1036 (CCPA 1979). Applicants did not contend in the prior Response (and do not assert now) that the Saatman and Wang references were "non-analogous art." Instead, Applicants showed that the skilled artisan would have no reason to modify the teachings of the cited references in order to arrive at the claimed methods. In fact, Applicants showed that the skilled artisan would have every reason to question whether the necessary modifications to the cited art would successfully result in the claimed methods. It appears that the Examiner has again mischaracterized Applicants' arguments and then dismissed them on the basis of that mischaracterization. Applicants again respectfully request that the prior arguments be reconsidered.

Thirdly, the Examiner maintained the rejection based in part on Schaeffer (Final Office Action, p. 3, ¶ 3). In the prior Office Action, Schaeffer was used to support the proposition that calpain inhibitors can be used to treat multiple sclerosis (MS). When combined with Saatman and Wang, Schaeffer was used to reject the claims that expressly recited axonal degeneration associated with MS. Since the claims that expressly recited MS have been canceled herein, the rejection over Saatman in view of Wang and Schaeffer is no longer applicable, or is at least cumulative with the rejection based on Saatman in view of Wang alone. As such, Applicants will address the rejection over Saatman in view of Wang herein.[1]

Lastly, the Examiner's comments in paragraph 4 of the Final Office Action dealt with the evidence presented in the Declaration of Dr. Bartus. Dr. Bartus had stated that AK295 was abandoned as a viable therapeutic for the treatment of neurodegeneration due to insufficient bioavailability. The Examiner discounted this expert's statements because Saatman demonstrated AK295 could be administered to animals to achieve a therapeutic result (although a different therapeutic result).

[1] In this same paragraph of the Final Office Action, the Examiner stated that "patients undergoing treatment for multiple sclerosis with AK295 would inherently be undergoing treatment for axonal degeneration." It must be stated that AK295 has not been used to treat MS and so no patient has undergone (inherently or expressly) such treatment.

Simply stating the fact that Saatman shows intra-arterial administration of AK295 protects animals against head trauma does not rebut or refute the declaratory evidence of Dr. Bartus. It seems that the Examiner's position is that because Saatman shows AK295 works *in vivo* in one situation (like head trauma), Dr. Bartus was wrong to believe that AK295 would not also work *in vivo* in different situations (like axonal degeneration). This is shocking since Dr. Bartus has extensive experience with AK295 and explained that he tested AK295 in various disease models like stroke, closed head injuries, and post-surgical brain trauma (Bartus Declaration, ¶ 7). Dr. Bartus is no doubt aware of what Drs. Powers and Glass explained in their declarations, namely, that head trauma and axonal degeneration involve different cell types, a different pathology, and they each have their own unique delivery challenges (*i.e.*, getting enough drug to the CNS for head trauma protection vs. getting enough drug to the PNS for treating axonal degeneration). Based on these facts and his own extensive experience, Dr. Bartus stated that he did not think it was possible to administer AK295 to an animal in a therapeutically practical manner to have sufficient bioavailability in the nervous system to have a significant effect on a condition such as peripheral neuropathy. So just because Saatman shows AK295 has some *in vivo* bioavailability for head trauma it does not mean that Dr. Bartus' skepticism of AK295 was wrong or deserves little weight. Reconsideration is respectfully requested, especially in light of Exhibits 2 and 7-9, which are discussed below.

Additional arguments regarding the rejection under § 103

Shortly after the Final Office Action was mailed the test for obviousness under 35 U.S.C. § 103 was taken up and reviewed by the U.S. Supreme Court in *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727 (April 30, 2007). In *KSR*, the Court reaffirmed the obviousness test provided in *Graham v. John Deere Co.*, 383 U.S. 1 (1966). *KSR*, 127 S.Ct. at 1734.

Graham v. John Deere Co., 383 U.S. 1 (1966) provides for four factual inquiries for making an obviousness determination under 35 U.S.C. § 103. These inquiries, or "Graham factors" as they are called, are: (1) determining the scope and content of the prior art; (2) ascertaining the differences between the prior art and the claimed subject matter; (3) resolving the level of ordinary skill in the pertinent art; and (4) evaluating evidence of secondary considerations. *Graham*, 383 U.S. at 17-18. Each of these factors is discussed below.

Level of Skill in the Art

The level of skill in the art is very high, such as a person having a MD or PhD degree in medicinal chemistry, neurology, or pharmacology, and at least several years of experience.

Scope and content of Saatman

Saatman deals with major trauma to the head, which is part of the central nervous system (CNS). Head-injured animals have major motor and cognitive dysfunction following injury. They lose many types of neurological cells in the brain following the injury. AK295 is disclosed as being neuro-protective after intra-arterial administration. Saatman does not disclose the use of AK295 for the treatment of axonal degeneration of the peripheral nervous system, much less chemically induced peripheral neuropathy. Saatman also does not indicate whether orally administered AK295 would have any effect for trauma to the head, let alone any disease like peripheral neuropathy.

Scope and content of Wang

Wang shows that AK295 is protective in two models of axonal degeneration. The first model is induced with vincristine and the second involves axotomy (cutting axons). The authors used DRG cultures and not whole animals. Wang does not teach the *in vivo* use of AK295 for treating axonal degeneration or peripheral neuropathy. Since *in vivo* use of AK295 is not disclosed, Wang is of course silent in regard to any particular route of administration to a patient.

Difference between the teachings of Saatman and Wang and the claims

The difference between the teachings of the cited references and the claims is the use of a genus of α-ketoamides, including AK295, for the treatment of axonal degeneration *in vivo*. This difference is deemed by the Examiner to be obvious in view of the cited references. Specifically, the Examiner has taken Saatman for the teaching that AK295 is active *in vivo* and Wang for the teaching that AK295 is effective for treating axonal degeneration *in vitro*. In combining these two teachings, the Examiner concludes that AK295 can be use *in vivo* for treating axonal degeneration—thus rendering obvious Applicants' claims. At first glance, such a combination of teachings may seem reasonable and the result may seem logical. However, this combination ignores pertinent facts and teachings from the references (not to mention pertinent secondary considerations) that would have made the combination of Saatman and Wang unreasonable and the result one that the skilled artisan would have expected to fail.

To simply allege that *in vivo* activity in one indication is reasonably suggestive of successful *in vivo* activity in another indication (even in light of evidence of *in vitro* activity for the other

indication) one must ignore the complexities of each indication. Such complexities, which would normally be considered by the skilled artisan, include differences in the compound's ability to get to its therapeutic target at effective concentrations in one indication versus its therapeutic target (often a different therapeutic target) at effective concentrations (often a different concentration) in another indication. The stability, metabolism, and selectivity must also be considered. Thus, one would not simply substitute one indication for another, even knowing of the compound's *in vitro* efficacy in the other indication.

Turning to the cited references, Saatman teaches of AK295's ability to protect against neuronal loss due to trauma. The neuronal cells protected are part of the CNS and are of course at an anatomically different location than cells of the PNS. The difference in location of the target cells between the two indications translates into a difference in pharmacological accessibility—a difference which is on the scale of the entire organism. Thus, the skilled artisan would not reasonably think that a compound which can reach the CNS will likewise reach cells of the organism's PNS. (This difference is even more pronounced when one tries to extrapolate the intra-arterial administration of Saatman to the oral administration recited in Claim 39.)

Moreover, the fact that Wang shows *in vitro* activity in axonal degeneration does not indicate similar activity *in vivo*. It goes without saying that the differences between a compound's ability to affect a cell *in vitro* versus *in vivo* are enormous. And while Saatman gives some assurance that the compound will at least be tolerated by an animal and it will have some effect (albeit in a different indication), the leap from Wang's *in vitro* experiments to an actual *in vivo* treatment for PN would not have been reasonably made by the skilled artisan with any expectation of success. Indeed, while Wang describes a cell based model of vincristine neurotoxicity (though not peripheral neuropathy), attempts by the inventors to develop an animal model of vincristine-induced neuropathy failed. Not until they experimentally examined other neurotoxic agents and arrived at Taxol could one test compounds in an animal model of PN. And even after the taxol-induced PN model was developed, it was not clear if AK295 would prevent axonal degeneration in this model (*see* the section on "skepticism of others" below). So even assuming the cited references suggest the claimed *in vivo* methods (which they don't), there is nothing in the references or elsewhere that would teach one how to even approach this problem. Therefore, the teachings of Saatman in light of Wang would not have given the skilled artisan any reason to expect AK295 would successfully treat PN.

Further, PN results from injury to axons due to treatment with neurotoxic agents or to diseases such as diabetes. It develops more slowly than a single traumatic injury to the central nervous system (*i.e.*, the brain and spinal cord). PN also more selectively affects axons and not the many types of tissues and cells injured in a head trauma. The neuronal cell body and the axon are biologically separate structures that respond differently to nervous system injury. Coleman, "Axon degeneration mechanism: commonality amid diversity," *Nat. Rev. Neurosci.*, 6(11):889-98, 2005 (provided in the previous Response). These differences in pharmacological accessibility on a cellular scale mean that one cannot assume Saatman's demonstrated effect in the CNS will translate to an effect on an axon in the PNS of a patient. In other words, those of skill in the art would understand that since the neuronal cell body and the axon are biologically separate structures that respond differently to various stimuli, treatment of neuronal cell trauma does not predict whether a compound would be effective in treatment of axonal degeneration for PN. Thus, not only is Saatman's teaching that a compound can affect the CNS of an organism not indicative of its affect on the organism's PNS, Saatman does not even suggest that the compound it can affect the particular part of a cell in the PNS, namely the axon.

In summary, the skilled artisan armed with the teachings of Saatman and Wang would have no reason to believe with any realistic expectation of success that an α-ketoamides like AK295 would treat axonal degeneration *in vivo*. They would naturally have had to contend with various complexities of developing a new therapy that cannot be assumed from the cited references. At best, the skilled artisan would view the cited references as neither favoring nor discouraging the use of AK295 for PN. But having no more of an expectation of AK295's success as its failure, there is simply no reasoning that supports the contention that treating PN with AK295 and like α-ketoamides is obvious.

Secondary considerations

Evidence of the long-felt but unsolved need, failure of others, skepticism of experts, *etc.* **must** be considered by the Examiner in determining issues of obviousness MPEP § 716.01(a). In addition to the Declarations already submitted, Applicants provide the following published statements from experts in the field regarding the claimed methods.

Long felt but unsolved need

First, the previously submitted Declarations of Drs. Powers and Glass discuss the long felt but unsolved need of providing a treatment for peripheral neuropathy. (Powers Declaration, ¶¶ 13-

15; Glass Declaration, ¶¶ 13-15). This evidence was not commented on by the Examiner. True, Drs. Powers and Glass are listed as inventors of the present application; however, their connection to this application should not result in little weight being given to their evidence on this point. It cannot reasonably be disputed that peripheral neuropathy is a major neurological illness affecting millions of people worldwide and an illness for which there is no treatment other than symptomatic palliation and occupational management.

In addition to these Declarations, consider Bouvcek, "Advanced Diabetic Neuropathy: A Point of no Return?" *Rev. Diabetic Stud.* 3:143-50, 2006 (Exhibit 1). The authors clearly state that treatment of peripheral neuropathy caused by diabetes has not yet been developed.

> Diabetic peripheral neuropathy is the most common complication of long-standing diabetes mellitus which frequently results in clinically significant morbidities *e.g.* pain, foot ulcers and amputations. . . . Unfortunately, to date, no treatment based on pathogenic considerations has shown clear positive effects and thus early institution of optimal glycemic control remains the only available measure with proven efficacy in preventing or halting progression of diabetic neuropathy. (Exhibit 1, Abstract.)

Additional evidence for a long felt but unsolved need can be found in the comments of the Reviewer on Dr. Glass' NIH Grant Proposal (Exhibit 2). These comments, released on October 27, 2003, state that "there is a tremendous need for treatment of peripheral neuropathies of all types, the potential that compounds identified by the proposal would be useful for multiple types of neuropathy" (Exhibit 2, p. 2, ¶ 1). The Reviewer goes on to state that:

> PN is a common side effect observed in the treatment of breast cancer patients with Taxol. Therefore, the identification of a drug that can selectively reduce PN while not interfering with the primary anti-cancer effects of Taxol would represent an important improvement in the treatment of breast cancer. (Exhibit 2, p. 2, ¶ 3.)

The Examiner is respectfully requested to consider these published statements from experts in the field as evidence of a long felt but unsolved need to treat peripheral neuropathy.

Failure of others

As evidence of the failure of others to treat peripheral neuropathy consider Wells and Bihovsky, "Calpain Inhibitors as potential treatments for stroke and other neurodegenerative diseases: Recent trends and developments," *Exp. Opin. Ther. Patents* 8(12):1707-27, 1998, (Exhibit 3). Here the authors review attempts by numerous researchers to develop calpain

inhibitors. The authors state that "[d]espite remarkable advances in understanding calpain's normal functions, as well as its involvement in neuropathological conditions, a full appreciation of its role in neuronal cells remains elusive. . . A drug candidate compound has yet to be identified for advancement to clinical testing." (Exhibit 3, Abstract.)

Also consider Liebetrau, "Calpain inhibitor A-558693 in experimental focal cerebral ischemia in rats," *Neurol. Res.* 27:466-70, 2005) (Exhibit 4). Liebetrau attempted to develop a calpain inhibitor carrying a ketoamide group, A-558693, for therapeutic purposes. He acknowledged that "calpain proteolysis plays an important role in the chain of events following cerebral ischemia. However, the calpain inhibitor A-558693 failed to prevent these changes." (Exhibit 4, Abstract.) Dr. Liebetrau went on to state that "[a]nother calpain inhibitor (AK295) was shown to be effective even several hours after initiation of cerebral ischemia. However, most of the investigated calpain inhibitors are not specific against calpain, and therefore the observed effect might be due to a broad inhibition of several proteases." (Exhibit 4, p. 466, col. 2, ¶ 2.)

Moore *et al.*, "Limited access trial using amifostine for protection against cisplatin and three hour paclitaaxel-induced neurotoxicity: a phase II study of the gynecologic oncology group," *J. Clinical Oncology*, 21(22):4207-13, 2003 (Exhibit 5), reported results from a study to determine whether amifostine (WR 2721) prevented or ameliorated clinically significant (grade 2 to 4) neurotoxcity associated with cisplatin and 3-hour paclitaxel chemotherapy. The authors found that "four of 27 assessable patients developed grade 2 to 4 neurotoxcity based on clinical assessments and CTC grading." (Exhibit 5, Abstract.) Because this number of neuropathetic patients exceeded the predetermined threshold level for a second stage of accrual, the study was closed. *Id.* The authors concluded that amifostine's level of activity was insufficient to warrant further study in a Phase III trial. *Id.*

Another failed attempt to treat peripheral neuropathy was based on ruboxistaurin. Adis R&D Profile, "Riboxistaurin, LY 333531," *Drugs* R D 8(3):193-9, 2007 (Exhibit 6) discusses ruboxistaurin, a compound under development by Eli Lilly as a therapy for, *inter alia*, diabetic peripheral neuropathy. After a randomized, double blind, parallel-group phase II study there were no significant differences between the ruboxistaurin and placebo groups. (Exhibit 6, p. 197, col. 2, ¶ 3.) Consequently Eli Lilly withdrew its marketing authorization application.

Wells and Bihovsky (Exhibit 3, discussed above) also state that "patent activity in the calpain field spans both reversible and irreversible inhibitors and it is still unclear which class is more likely to produce a therapeutically useful drug" (Exhibit 3, p. 1710, ¶ 3).

The Examiner is respectfully requested to consider these published statements from experts in the field as evidence of the failure of others to treat peripheral neuropathy.

Specific criticism/skepticism of others about AK295

As noted above, the Declaration of Dr. Bartus provides specific evidence regarding skepticism of others about the use of AK295. Reconsideration of this evidence is respectfully requested.

As additional evidence consider Lubisch *et al.*, "Benzoylalanine-derived ketoamides carrying vinylbenzyl amino residues: discovery of potent-water soluble calpain inhibitors with oral bioavailability," *J. Med Chem.* 46:2404-12, 2003 (Exhibit 7). Here the authors specifically discussed the reversible inhibitors MDL 28170 and AK-295, which have the dipeptides Z-Val-Phe and Z-Leu-Abu, respectively, as backbone and either an aldehyde or ketoamide moiety as reactive moiety. Lubisch *et al.* stated:

> In general, using such aldehyde and ketone moieties as reactive moiety can give rise to problems with respect to stability, metabolism, and selectivity. . . The ketoamide AK295, which is one of the first water soluble reversible calpain inhibitors, is only effective when administered via special route. Efforts to discover an appropriate surrogate for the highly reactive aldehyde or ketone as a reactive moiety have been unsuccessful. . . Moreover, there have been few reports of calpain inhibitors exhibiting the oral activity which is required for them to be used in some of the envisaged therapies. Hence, the use of the calpain inhibitors so far reported is limited for one or more of the following reasons: poor selectivity, poor metabolic stability, low cellular penetration, poor kinetics, and depending on the envisaged therapeutic indication, low oral bioavailability and low water solubility. (Exhibit 7, p. 2404-05.)

Lubisch *et al.* clearly expresses the skepticism in the art regarding the use of AK295. Moreover, Lubisch *et al.* even addresses the data in the Saatman reference, which was cited by the Examiner in the present rejection. Specifically, the authors state:

> Calpain inhibitors were suggested as useful agents in the treatment of traumatic brain injury (TBI). After experimental traumatic brain injury, substantial loss of cytoskeletal proteins was observed which was attributed to enhanced calpain activity. Furthermore, the calpain

> inhibitor AK295 attenuated motor and cognitive deficits following experimental brain injury in rats [citing Saatman]. However, these studies gave rise to controversial data since injury-induced spectrin breakdown and cortical lesions size were not affected by AK295. This is remarkable since a decrease in spectrin degradation is often used as a marker of calpain inhibition *in vitro* and *in vivo*. (Exhibit 7, p. 2408, col. 1, ¶ 5.)

The skepticism in the art regarding AK295 was even reflected in the Reviewer's comments on Dr. Glass' NIH Grant Proposal (Exhibit 2, discussed above). The Reviewer stated that "[t]he major weakness of the application was that the lead compound appears to have too low an *in vivo* potency to be a very good candidate and the second generation compounds appeared to be even less potent." (Exhibit 2, p. 2, ¶ 1.) The Reviewer also stated that:

> There are a number of concerns regarding the *in vivo* properties of AK-295, and its structural congeners, that diminish the level of enthusiasm for this proposal. The first (and major) concern is related to the ability of AK295 to cross the cell membrane and inhibit calpain *in vivo*. For example, the Ki of AK295 for inhibiting calpain II *in vito* is 41 nM. However, the IC50 for inhibiting calpain II in cell culture (*i.e.*, the platelet membrane permeability assay) is 45 μM, which represents a 1000 fold lower potency in the cell culture assay (*i.e.*, the IC50 platelet permeability assay /Ki *in vitro* ratio = 1097). . . . The low cellular uptake of AK295 is also consistent with the high doses required to demonstrate activity in the mouse model of Taxol-induced PN (48 mg/kg s.c. or 24 mg/kg/day using an Alzet minipump delivery system). Since this compound is likely to be excreted rapidly through the hepatobilliary and renal systems, the oral dose of AK295 is predicted to be much higher and will likely lead to tissue toxicity in these organs. In addition, the second generation compounds (18, 19, and 35) are likely to have a lower in vivo potency since the IC50 platelet permeability assay/Ki *in vitro* ratios are 1364 (compound 18), 4600 (compound 19), and 6470 (compound 35). (Exhibit 2; p. 3, ¶ 2.)

Further, there was significant doubt in the art regarding the use of AK295 and similar compounds in humans due to uncertainty surrounding whether such compounds could penetrate the blood-brain and/or blood-nerve barrier. See, for example, Bartus *et al.*, "Calpain inhibitor AK295 protects neurons from focal brain ischemia," *Stroke* 25(11):2265-70, 1994 (Exhibit 8), which reports the use of AK295 to treat stroke model by intra-arterial administration. On page 2270 of Exhibit 8, the Editor remarks that because AK295 is water soluble, "[o]ne presumes, therefore, that it may not penetrate an intact blood brain barrier. It is therefore possible that its effectiveness may

be greater if it is administered after the ischemia has had time to break down the blood brain barrier, thereby allowing penetration of the drug into the ischemic brain."

Even after resubmitting the grant application and addressing the Review's Comments, there was still doubt by these experts in the field. In particular, the Review Comments released on August 11, 2004 (Exhibit 9), the Reviewer stated that:

> Although the proposed research contains some strong points, there are a number of concerns regarding the *in vivo* properties of AK295, and its structural congeners, that diminish the level of enthusiasm for this grant proposal. . . . The first and major concern is the ability of AK295 to cross an intact cell membrane and inhibit calpain *in vivo*. . . . AK295 appears to have [marginal protective effect] in the taxol neuropathy mouse model (Figures 1 and 2). This marginal effect is likely related to the poor cell permeability of this class of compounds, which is a common feature of peptide-based enzyme inhibitors. The concentration of 50 μM concentration needed in the cell culture assays to demonstrate and effect in Figure 3 only adds further support that these compounds are likely to have a marginal effect in preventing PN *in vivo*. (Exhibit 9, p. 3, ¶¶ 2-3).

Since the NIH grant reviewers, who are experts in the field, stated that they did not believe that AK295 could be used with any expectation of success, and neither did Dr. Bartus and Lubisch *et al.*, then this evidence clearly and unequivocally show that experts in the field had serious doubts about whether AK295 could be used to treat peripheral neuropathy. Accordingly, the statements highlighted in these documents alone (not to mention in combination with the other evidence submitted herewith) should indicate the non-obviousness of Applicants' claimed methods.

CONCLUSION

In view of the foregoing amendments, arguments, secondary considerations, and enclosed exhibits it is respectfully submitted that the Office Action has failed to sufficiently establish that the claimed methods of treating axonal degeneration were obvious to one of ordinary skill in the art. Thus, Applicants respectfully request that the rejections under 35 U.S.C. § 103 be withdrawn.

Applicants also note that dependent claim 39, which recites oral administration, is patentable for the additional reason that nowhere in the cited references is oral administration of AK295 suggested. Saatman's *in vivo* administration is via inter-arterial injection. And the lack of teaching of oral administration, coupled with the expressed skepticism of experts in the field

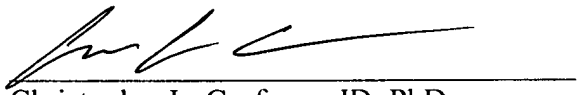
regarding the perceived lack of oral bioavailability (*see e.g.*, Exhibit 2, p. 2, ¶ 2; Exhibit 7, p. 2404-05; and Exhibit 9, p. 3, ¶¶ 2-3), indicates that this claim is not obvious.

The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A Credit Card Payment Form PTO-2038 authorizing payment in the amount of $930.00, which includes the fee for a small entity under 37 C.F.R. § 1.17(a)(3) for a Thee-Month Extension of Time and the fee for a small entity under 37 C.F.R. § 1.17(e) for the RCE is enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Deposit Account No. 14-0629.

Respectfully submitted,

NEEDLE & ROSENBERG, P.C.

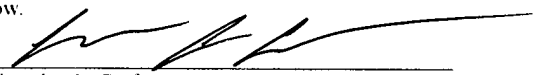


Christopher L. Curfman, JD, PhD
Registration No. 52,787

NEEDLE & ROSENBERG, P.C.
Customer Number 23859
(678) 420-9300 Phone
(678) 420-9301 Facsimile

CERTIFICATE OF MAILING UNDER 37 CFR § 1.8

I hereby certify that this correspondence and the documents mentioned therein are being deposited with the United States Postal Service in an envelope addressed to: MAIL STOP RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA. 22313-1450, on the date indicated below.



Christopher L. Curfman

February 6, 2008
Date